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# A link between KIT expression, mast cell abundance and activity, and Th2-high endotype in asthmatic airways

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**Background**

Emerging evidence indicates that mast cells infiltrate the epithelial layer in asthma patients. This infiltration is associated with airway hyperresponsiveness in nitric oxide-high asthma phenotype, suggesting a link between mast cells with Th2-high endotype. High dose of budesonide have been showed to decreased airway hyperresponsiveness, which correlates with a reduction of mast cells number. The development, proliferation, and survival of human mast cells depend crucially on KIT (CD117), a transmembrane receptor tyrosine kinase. In clinical trials, the tyrosine kinase inhibitors imatinib and masitinib, which also inhibit KIT, have benefited severe asthma patients who were unresponsive to high-dose corticosteroids. These benefits are likely due to the inhibitors' effects on mast cell numbers and functions, which depend on KIT. However, a comprehensive analysis of *KIT* expression in diverse asthma populations remains lacking. This study aims to bridge this gap through an in-depth bioinformatic analysis of *KIT* expression by ultilizing the publicly available datasets.

**Methods**

We curated five gene expression datasets from NCBI-GEO (GSE41861, GSE43696, GSE63142, GSE67472, and GSE89809) featuring bronchial epithelial brushing samples from patients with asthma and healthy subjects. Additionally, we included two other datasets (GSE76226 and GSE65584) derived solely from epithelial brushing samples from asthma patients to compare KIT-high and KIT-low asthma groups. We assessed *KIT* or other gene expressions, immune cell abundance, and activity of immune-related signaling pathways. We classified the samples to Th2-high and Th2-low asthma endotypes according to IL13-induced genes in bronchial epithelial cells (*CLCA1*, *POSTN*, and *SERPINB2*) and explored their associations with KIT.

**Results**

Patients with asthma showed elevated *KIT* expression ($p < 0.001$) in four out of five (4/5) datasets. The abundance of mast cells, Th2 cells, and basophils was higher in patients with asthma compared to normal subjects ($p < 0.05$ in 5, 3, and 2/5 datasets, respectively), as examined by two different in silico cytometry methods. The KIT-high asthma group displayed increased mast cell and basophil abundance ($p < 0.001$ in 6/7 and $p < 0.01$ in 4/7 datasets, respectively) and elevated activity in Fc$\varepsilon$RI, interleukin, and TGF$\beta$ family signaling pathways compared to the KIT-low asthma group. We found that KIT expression and mast cell abundance was positively

associated with Th2-high asthma endotype ($p < 0.05$ in 7/7 datasets).

**Conclusions**

Our comprehensive analysis underscores the elevated expression of KIT in asthma patients. The positive correlation of KIT with mast cell abundance and activation, inflammatory signaling pathways, and the Th2-high asthma endotype may highlight KIT and/or mast cell as important drivers and therapeutic targets for asthma.

Tran, N.Q.V., Le, M.-K., Nakamura, Y., Kondo, T. and Nakao, A. (2024), A link between KIT expression, mast cell abundance and activity, and Th2-high endotype in asthmatic airways. Allergy, 79: 1338-1342. https://doi.org/10.1111/all.15954