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جامعة الملك سعود
King Saud University

Effect of LCK Inhibition on Airway Inflammation in Allergic Mouse Model of Asthma

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INTRODUCTION

Asthma is a chronic inflammatory pulmonary disease with a world-wide prevalence in which different immune/non-immune cells, e.g., T cells, eosinophils, macrophages, epithelial cells play a significant role[1]. These immune cells interact among themselves eventually causes characteristic features of asthma, *i.e.,* airway inflammation, mucus hypersecretion, and airway hyperresponsiveness[1,2]. T cells are reported to be significant contributors to allergic airway inflammation through release of multiple mediators such as cytokines and oxidants which are controlled by several kinases, one of them being Lymphocyte-specific protein tyrosine kinase (Lck)[3-5]. Lck has been reported to be crucial for expression/production of several key inflammatory cytokines through modulation of several other kinases/transcription factors in T cells[3-5]. However, role of Lck remains unexplored in allergic asthma.

OBJECTIVES

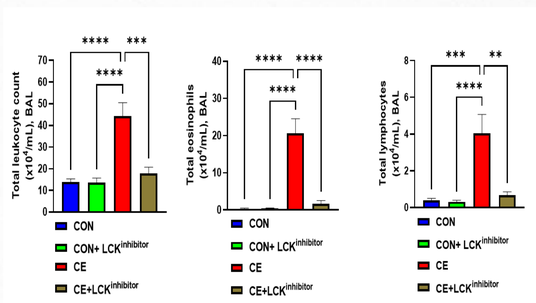
- The aim of this study was to determine the role of LCK in allergic (Th2/eosinophilic) murine model of asthma
- In addition, this study evaluated the effect of LCK inhibition on allergic (Th2/eosinophilic) airway inflammation

METHODS

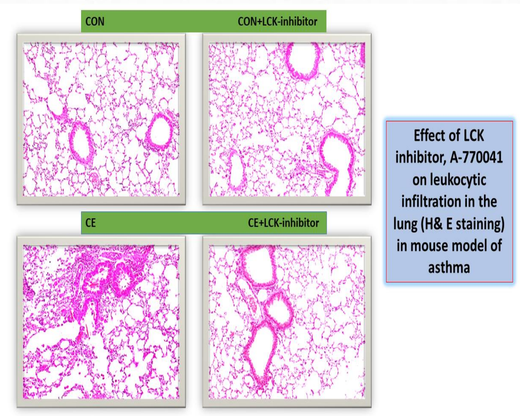
- Male C57/BL6 mice, 8-10 weeks of age, and weigh 20-25 gram were used in this study.
- Allergic asthma was induced by whole-body German cockroach extract (CE) (Blattella germanica; Greer Laboratories; Lenoir, NC, USA)
- Mice were sensitized with 50 µg CE/mouse in saline on days 1-5 intranasally (i.n.). After ten days, the mice were challenged with 50 µg of CE/mouse on days 11-15[6,7].
- LCK inhibitor, A-770041 was administered intranasally (i.n.) for 5 days (day 11-15) at a dose of 10 mg/kg.
- Bronchoalveolar lavage (BAL) was performed on day 16 for assessment of Total leukocyte count (TLC) and differential leukocyte count (DLC).
- Flow cytometry was performed in pulmonary single cell suspension for assessment of p-LCK, IL-4, iNOS, and Nitrotyrosine
- ELISA Kit was used to determine Th2 related protein, IL-4
- Lung was fixed in 10% formalin for histopathological assessment (H&E staining)
- Statistical analysis: Data are represented as Mean ± SEM (n=5-6). Comparisons among different groups were conducted using ANOVA followed by Tukey's multiple comparison test. $P<0.05$ was considered as significant.

RESULTS

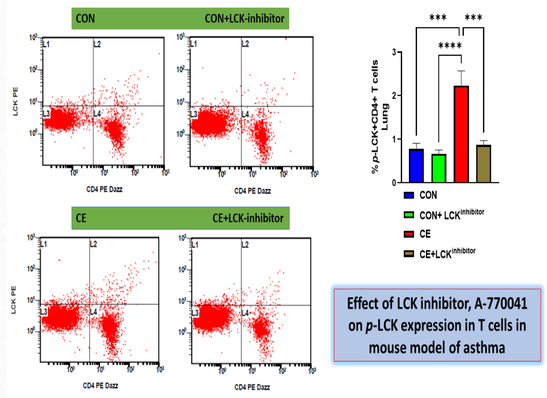
- Allergen challenge (CE) causes activation of LCK in T cells, *i.e.*, p-LCK.
- Airway inflammation is reduced by LCK inhibitor in CE-induced murine model of asthma
- Activation of LCK, *i.e.,* p-LCK is reduced in T cells by LCK inhibitor in CE-induced murine model of asthma
- Allergic cytokine, IL-4 is reduced in T cells/lung by LCK inhibitor in CE-induced murine model of asthma
- Oxidative stress markers such as iNOS and nitrotyrosine in T cells are reduced by LCK inhibitor in CE-induced murine model of asthma



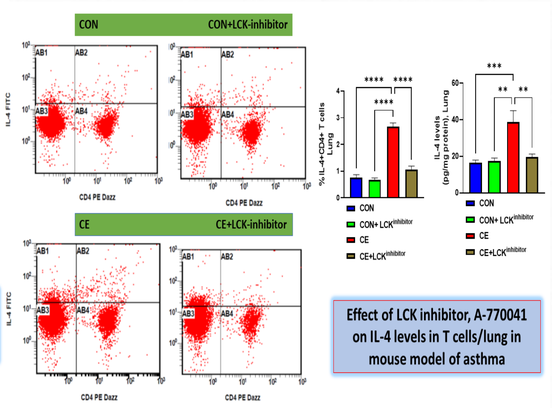
Effect of LCK inhibitor, A-770041 on Allergic airway inflammation in mouse model of asthma



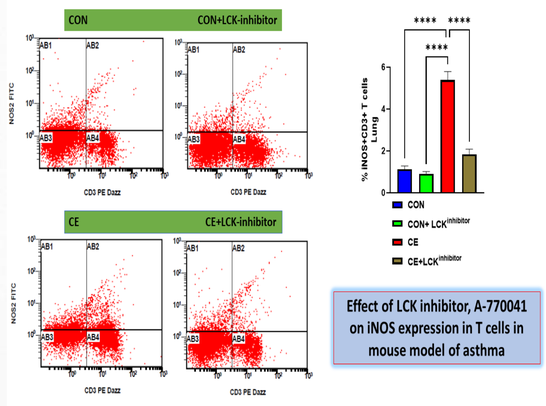
Effect of LCK inhibitor, A-770041 on leukocytic infiltration in the lung (H& E staining) in mouse model of asthma



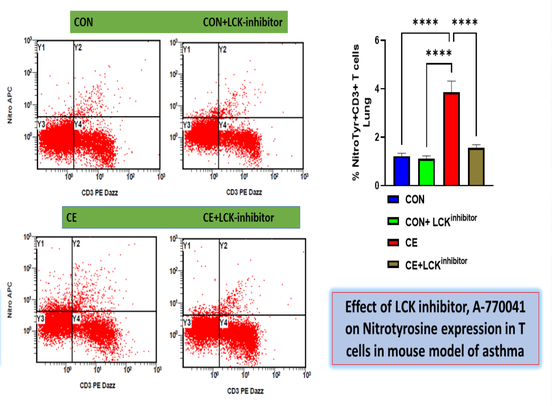
Effect of LCK inhibitor, A-770041 on *p*-LCK expression in T cells in mouse model of asthma



Effect of LCK inhibitor, A-770041 on IL-4 levels in T cells/lung in mouse model of asthma



Effect of LCK inhibitor, A-770041 on iNOS expression in T cells in mouse model of asthma



Effect of LCK inhibitor, A-770041 on Nitrotyrosine expression in T cells in mouse model of asthma

DISCUSSION and CONCLUSIONS

- Downregulation of *p*-LCK by LCK inhibitor is associated with reduction of airway inflammation, allergic cytokines, and oxidative stress
- LCK inhibition may be a potential therapeutic strategy to counteract airway inflammation in asthma

REFERENCES

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