Glutamine deficiency shifts the asthmatic state toward neutrophilic airway inflammation

June-Mo Kim¹, Yoo-Na Im¹, Yun-Jo Chung², Jung-ho Youm¹, Suhn-Young Im³, Myung Kwan Han¹, and Hern Ku Lee¹

¹Jeonbuk National University Medical School
²Jeonbuk National University
³Chonnam National University

July 21, 2021

Abstract

Background: The administration of L-glutamine (Gln) suppresses allergic airway inflammation via the rapid upregulation of MAPK phosphatase (MKP)-1, which functions as a negative regulator of inflammation by deactivating p38 and JNK mitogen-activated protein kinases (MAPKs). However, the role of endogenous Gln remains to be elucidated. Therefore, we investigated the mechanism by which endogenous Gln regulates MKP-1 induction and allergic airway inflammation in an ovalbumin-based murine asthma model. Methods: We depleted endogenous Gln levels using l-γ-glutamyl- p-nitroanilide (GPNA), an inhibitor of the Gln transporter ASCT2, and glutamine synthetase small interfering (si)RNA. Lentivirus expressing MKP-1 was injected to achieve overexpression of MKP-1. Asthmatic phenotypes were assessed using our previously developed ovalbumin-based murine model, which is suitable for examining sequential asthmatic events, including neutrophil infiltration. Gln levels were analyzed using a Gln assay kit. Results: GPNA or glutamine synthetase siRNA successfully depleted endogenous Gln levels. Importantly, homeostatic MKP-1 induction did not occur at all, which resulted in prolonged p38 MAPK and cytosolic phospholipase A2 (cPLA2) phosphorylation in Gln-deficient mice. Gln deficiency augmented all examined asthmatic reactions, but it exhibited a strong bias toward increasing the neutrophil count, which was not observed in MKP-1-overexpressing lungs. This neutrophilia was inhibited by a cPLA2 inhibitor and a leukotriene B4 inhibitor, but not by dexamethasone. Conclusion: Gln deficiency leads to the impairment of MKP-1 induction and activation of p38 MAPK and cPLA2, resulting in the augmentation of neutrophilic, more so than eosinophilic, airway inflammation.

Hosted file

Gln defi_manuscript x-unmarked.docx available at https://authorea.com/users/426899/articles/531244-glutamine-deficiency-shifts-the-asthmatic-state-toward-neutrophilic-airway-inflammation

Hosted file

Gln_defi_Figure x Unmarked.pptx available at https://authorea.com/users/426899/articles/531244-glutamine-deficiency-shifts-the-asthmatic-state-toward-neutrophilic-airway-inflammation