Glutamine deficiency shifts the asthmatic state toward neutrophilic airway inflammation

June-Mo Kim[1], Yoo-Na Im[1], Yun-Jo Chung[2], Jung-ho Youm[1], Suhn-Young Im[3], Myung Kwan Han[1], and Hern Ku Lee[1]

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

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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 A $_2$ (cPLA $_2$) 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 cPLA $_2$ 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 cPLA $_2$, resulting in the augmentation of neutrophilic, more so than eosinophilic, airway inflammation.

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