Gasdermin B, an asthma-susceptibility gene, promotes MAVS-TBK1 signalling and airway inflammation

Tao Liu[1], Siqi Liu[1,7], Xianliang Rui[1,7], Ye Cao[2], Julian Hecker[1], Feng Guo[1], Yihan Zhang[3], Lu Gong[1], Yihan Zhou[1], Yuzhen Yu[1], Nandini Krishnamoorthyni[4], Samuel Bates[1], Sung Chun[5], Nathan Boyer[1], Shuang Xu[1], Jin-Ah Park[6], Mark A. Perrella[4], Bruce D. Levy[4], Scott T. Weiss[1], Hongmei Mou[3], Benjamin A. Raby[1,4,5,8] and Xiaobo Zhou[1,8]

[1]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. [2]Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. [3]The Mucosal Immunology and Biology Research Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. [4]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. [5]Division of Pulmonary Medicine, Department of Pediatrics, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA. [6]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [7]These authors contributed equally. [8]These authors jointly conceptualised and supervised this work.

Corresponding author: Xiaobo Zhou (xiaobo.zhou@channing.harvard.edu)

Shareable abstract (@ERSpublications)
Asthma GWAS gene *GSDMB* promotes the induction of *ISGs*, mucus production and lung inflammation post-respiratory virus infection *in vivo*. In cellular models, *GSDMB* recognises and binds viral RNA, thereby activating viral RNA-induced MAVS-TBK1 signalling. https://bit.ly/48CVGxC

Cite this article as: Liu T, Liu S, Rui X, *et al*. Gasdermin B, an asthma-susceptibility gene, promotes MAVS-TBK1 signalling and airway inflammation. *Eur Respir J* 2024; 63: 2301232 [DOI: 10.1183/13993003.01232-2023].

This article has an editorial commentary: https://doi.org/10.1183/13993003.02223-2023

Received: 3 March 2023
Accepted: 31 Dec 2023

Abstract

Rationale Respiratory virus-induced inflammation is the leading cause of asthma exacerbation, frequently accompanied by induction of interferon-stimulated genes (*ISGs*). How asthma-susceptibility genes modulate cellular response upon viral infection by fine-tuning *ISG* induction and subsequent airway inflammation in genetically susceptible asthma patients remains largely unknown.

Objectives To decipher the functions of gasdermin B (encoded by *GSDMB*) in respiratory virus-induced lung inflammation.

Methods In two independent cohorts, we analysed expression correlation between *GSDMB* and *ISGs*. In human bronchial epithelial cell line or primary bronchial epithelial cells, we generated *GSDMB*-overexpressing and *GSDMB*-deficient cells. A series of quantitative PCR, ELISA and co-immunoprecipitation assays were performed to determine the function and mechanism of *GSDMB* for *ISG* induction. We also generated a novel transgenic mouse line with inducible expression of human unique *GSDMB* gene in airway epithelial cells and infected the mice with respiratory syncytial virus to determine the role of *GSDMB* in respiratory syncytial virus-induced lung inflammation *in vivo*.

Results *GSDMB* is one of the most significant asthma-susceptibility genes at 17q21 and acts as a novel RNA sensor, promoting mitochondrial antiviral-signalling protein (MAVS)-TANK binding kinase 1 (TBK1) signalling and subsequent inflammation. In airway epithelium, *GSDMB* is induced by respiratory viral infections. Expression of *GSDMB* and *ISGs* significantly correlated in respiratory epithelium from two independent asthma cohorts. Notably, inducible expression of human *GSDMB* in mouse airway epithelium led to enhanced *ISGs* induction and increased airway inflammation with mucus hypersecretion upon respiratory syncytial virus infection.

Conclusions *GSDMB* promotes *ISGs* expression and airway inflammation upon respiratory virus infection, thereby conferring asthma risk in risk allele carriers.