Inflammatory on and off switch identified for allergic asthma and COPD

August 1 2013

Japanese researchers have made a new step toward understanding why—and how to stop—runaway inflammation for both chronic obstructive pulmonary disorder (COPD) and allergic asthma. In a new report appearing in the August 2013 issue of *The FASEB Journal* scientists show that two receptors of an inflammatory molecule, called "leukotriene B4," play opposing roles in turning inflammation on and off for allergic asthma and COPD. The first receptor, called "BLT1," promotes inflammation, while the second receptor, called "BLT2," has a potential to weaken inflammation during an allergic reaction. This discovery also is important because until now, BLT2 was believed to increase inflammatory reaction.

"Leukotriene B4 levels are elevated in the airways of the patients with asthma and COPD, and the opposite role of BLT1 and BLT2 in allergic inflammation implies that drug development should target BLT1 and BLT2 differently," said Hiromasa Inoue, M.D., study author from the Department of Pulmonary Medicine at the Graduate School of Medical and Dental Sciences at Kagoshima University in Kagoshima, Japan. "We hope that better anti-asthma drugs or anti-COPD drugs will be produced in the future to treat millions of patients who suffer from severe asthma and COPD."

To make this discovery, scientists compared the allergic reactions in BLT2-gene deleted mice to those in normal mice. Then an allergic asthma reaction was provoked by inhalation of allergens. BLT2-gene deleted mice showed more inflammatory cells in the lung compared to

normal mice. Without the BLT2 gene, lung allergic inflammation was stronger than that of normal mice. The production of interleukin-13, an important mediator of allergic inflammation from T lymphocytes, was increased in the group without the BLT2 gene. Results suggest that targeting these two receptors differently and/or separately could achieve vastly different outcomes. Conventional anti-leukotriene B4 drugs block both of the pathways induced by BLT1 and BLT2. By manipulating the specific target, it may be possible to develop more effective anti-leukotriene B4 drugs.

"This is one case where BLT isn't a sandwich! Distinguishing between BLT1 and BLT2 is an important step forward to developing more effective drugs for lung inflammation," said Gerald Weissmann, M.D., Editor-in-Chief of *The FASEB Journal*. "Understanding the specific roles of these and other receptors allow researchers to identify new drug targets, which in turn can lead to new and more effective drugs."

More information: Yuko Matsunaga, Satoru Fukuyama, Toshiaki Okuno, Fumiyuki Sasaki, Takehiko Matsunobu, Yukari Asai, Koichiro Matsumoto, Kazuko Saeki, Masahiro Oike, Yukari Sadamura, Kentaro Machida, Yoichi Nakanishi, Masato Kubo, Takehiko Yokomizo, and Hiromasa Inoue. Leukotriene B4 receptor BLT2 negatively regulates allergic airway eosinophilia. *FASEB J* August 2013 27:3306-3314; doi:10.1096/fj.12-217000