MAP(kinase)-ing a Link between Obesity and Inflammation in Severe Asthma

Severe asthma is a considerable clinical problem that causes substantial morbidity and mortality for patients and a high economic burden. Approximately 10% of all patients with asthma suffer from the severe form, which the Global Initiative for Asthma 2018 defines as disease that is uncontrolled by therapy or is only controlled by two or more controller medications (such as long-acting β2-agonists and inhaled corticosteroids) and additional reliever therapy (e.g., short-acting β2-agonists) (1). Severe asthma accounts for a disproportionate use of resources (2) and remains an area of substantial unmet clinical need.

Obesity is a global public health problem of rapidly increasing prevalence (3). Obesity has profoundly negative effects on health. In addition to links with cardiovascular disease and type II diabetes, obesity is a risk factor for the development of asthma, and many reports have suggested a link between obesity and increases in both asthma severity and exacerbations (4). Interestingly, cluster analyses of subjects with asthma have highlighted an obese asthma phenotype that is characterized by late onset of disease with a predominance in females, higher disease burden, and altered airway inflammation with low numbers of eosinophils but high numbers of neutrophils (5).

Obesity has been associated with a chronic inflammatory response for many years (6); however, a direct link between obesity, dietary fat intake, and altered innate immune responses in asthma was first described by Kim and colleagues in 2014 (7). In that study, mice fed a high-fat diet developed airway hyperresponsiveness that

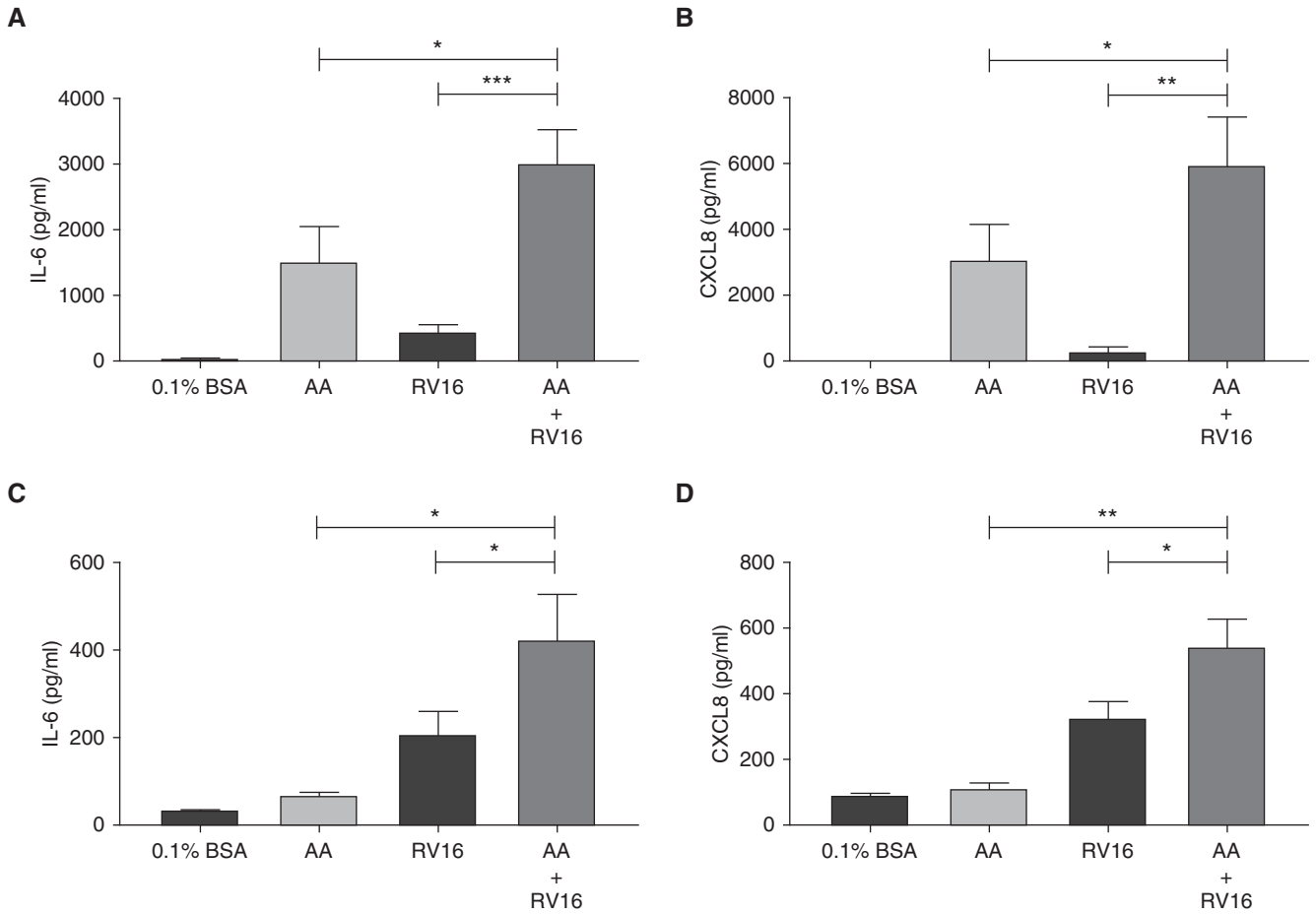

Figure 1. Synergistic effect of arachidonic acid (AA) and viral infection on IL-6 and CXCL8 release in primary lung fibroblasts and BEAS-2B cells. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. RV16 = rhinovirus 16.

was dependent on innate, but not adaptive, immunity. Obesity has also been linked with increased frequency of asthma exacerbations (8). However, until now, the mechanisms driving the association between obesity and increased asthma exacerbations, particularly in response to pulmonary infections, and whether dietary fatty acids are involved, have not been explored.

In this issue of the *Journal*, Rutting and colleagues (pp. 554–568) describe a novel role for dietary fatty acids in mediating innate immune responses to respiratory infections, with differential effects on lung fibroblasts and epithelial cells (9) (Figure 1). They convincingly demonstrate that dual treatment of primary human lung fibroblasts with either the viral mimetic polyinosinic:polycytidylic acid or the bacterial compound lipoteichoic acid and the polyunsaturated fatty acid (PUFA) arachidonic acid (ω-6 PUFA) causes a synergistic response in terms of the release of IL-6 and CXCL8, two cytokines that are known to have important roles in severe asthma (10, 11). Similar responses were observed in the BEAS-2B epithelial cell line.

In addition to showing an effect of PUFAs on inflammatory responses to pathogen components, Rutting and colleagues investigated the specific signaling pathways involved using selective pathway inhibitors. The authors demonstrate for the first time that the combined effects of arachidonic acid and pathogen treatment on IL-6 and CXCL8 release were mediated by p38 mitogen-activated protein (MAP) kinase signaling and prostaglandins in lung fibroblasts. However, the cytokine responses were independent of prostaglandins in BEAS-2B cells (9), highlighting the differential pathways in the two cell types. The identification of a role for p38 MAP kinase in increasing the inflammatory response to infection in the presence of increased fatty acids is fascinating because this pathway is known to be involved in other obesity-related pathologies, including type II diabetes (12), raising the possibility of potential crossover in disease pathogenesis. Finally, the authors confirmed the synergistic effect of arachidonic acid on infection-induced IL-6 and CXCL8 release in an *in vitro* live rhinovirus infection model to replicate their findings using pathogen components (9).

Taken together, these novel findings suggest that increased levels of PUFAs may lead to an exacerbated inflammatory response to respiratory infection, which could have important implications for exacerbations and disease burden in obese individuals with asthma. The study is somewhat limited by its sole reliance on *in vitro* cell models to study respiratory infection, and it will be important to see future research directed toward confirming the importance of the p38 MAP kinase pathway in mediating altered immune responses to pathogens in the presence of dietary fatty acids using *in vivo* animal models. Moreover, it is important to determine whether the findings of this study in the BEAS-2B cell line can be replicated in primary bronchial epithelial cells.

Fundamentally, these studies provide important groundwork for identifying the signaling pathways that are involved in altered innate immune responses to infections in obesity, and potentially shed light on the link between obesity and the increased number of asthma exacerbations in patients with severe asthma (8). ■

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