Editorial
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Resveratrol in Asthma: A French Paradox?

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Asthma is a chronic disorder of the airway which is characterized by variable and recurrent symptoms, such as reversible airflow obstruction, wheezing, and coughing. Asthma becomes one of the major public health problems, and more than 330 million people worldwide have asthma. Asthmatics have an exaggerated response to allergens, which leads to the activation of both innate and acquired immune systems. From an immunological point of view, asthma is mediated by hyperactivation of Th2 cells, IgE production, and eosinophilia.[1] Besides secretion of conventional Th2 cytokines, oxidative stress contributes to the development of asthma. For example, reduced intake of antioxidants, such as vitamin E, vitamin D, selenium, zinc, and PUFA has been invoked to explain the increase of asthma prevalence in Western countries.[2,3] Airway inflammatory cells, such as macrophages, eosinophils, and neutrophils, from patients with asthma release increased quantities of reactive oxygen species compared to health subsets.[4] The excessive quantities of reactive oxygen result in various pathophysiologic features of asthma, including airway smooth muscle contraction, airway hyperreactivity (AHR), mucus hypersecretion, epithelial shedding, and vascular exudation.[2] In addition, ROS stimulates airway inflammation by activating redox-sensitive transcription factors, such as NF-κB, JAK-STAT, and Raf-1.[2] Taken together, these results clearly demonstrate that oxidative stress can exacerbate asthma symptoms, while antioxidant supplements may reduce them.

Resveratrol (trans-3,4,5-trihydroxystilbene) is a form of natural phenol, produced by several plants in response to injury. The natural sources of resveratrol are skin of grapes, several berries, and senna.[5] In this issue, Lee *et al.*[6] reported the therapeutic effects of resveratrol in a murine model of allergic asthma. They showed that oral administration of resveratrol efficiently suppressed ovalbumin (OVA)-induced airway inflammation and remodeling. Several studies demonstrated that resveratrol and other plant-derived polyphenol could inhibit airway inflammation and AHR in various murine models of asthma. First, studies using a murine model of allergic asthma reported the inhibitory effect of resveratrol. In a model of OVA-induced asthma, OVA-specific IgE, IgG2a, as well as Th2 inflammatory cytokines, such as IL-4 and IL-5, was significantly reduced by resveratrol treatment. Moreover, oral administration of resveratrol suppressed the development of AHR, eosinophilia, and mucus hypersecretion.[7] Another study using OVA as an allergen showed similar results. The mice treated with resveratrol decreased tissue inflammation compared to vehicle-treated mice.[8] In addition, they showed that resveratrol treatment resulted in reduced subepithelial collagen deposition compared to vehicle-treated mice.[8] Second, in a murine model of house dust mite -induced asthma, resveratrol obviously reduced the level of TNF-alpha in BAL fluid, fibrotic response and airway inflammation.[9] Also, resveratrol inhibited the expression of the Syk protein and degranulation in mast cells.[9] Third, the inhibitory role of resveratrol is evaluated in an obesity-associated allergic pulmonary inflammation.[10] The mice fed with a high-fat diet (HFD) or a standard chow diet were challenged with OVA to induce asthma. OVA challenge in HFD-fed mice increased eosinophil infiltration in the BAL fluid compared to lean mice, and resveratrol treatment almost abrogated eosinophil infiltration in the obese mice.[10] The models reviewed above clearly showed that although resveratrol inhibits the process of inflammation, mechanisms for resveratrol have not yet been elucidated.

Interestingly, in this issue Lee *et al.*[6] showed that resveratrol treatment suppressed epithelial-mesenchymal transition (EMT) markers, such as snail, slug, vimentin, and α-SMA. EMT is known to be induced by various environmental factors, and oxidative stress is one of the main triggers of EMT. Also, transforming growth factor β1 (TGF-β1) is a major driving force of the EMT process.[11] In asthma, airway remodeling involves dif-

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ferentiation of airway epithelial cells into myofibroblasts *via* EMT which increases collagen and matrix synthesis. Despite many results indicating that EMT can be a target for resveratrol, little is known about the role of resveratrol on EMT occurring in airway epithelial cells. Therefore, elucidation of mechanisms for the prevention and/or reversal of TGF-β1-induced EMT may be important for suppressing the development of asthma. In current issue, Lee *et al.*[7] showed that resveratrol treatment could reduce the expression of TGF-β1/phosphorylated Smad2/3 in the cells from BAL fluid as well as in the epithelial cells. Thus, this signaling pathway could explain one of the inhibitory mechanisms of resveratrol. Although several studies including Lee *et al.* have shown the therapeutic effects of resveratrol in the settings of asthma, it is still unclear how resveratrol can reduce airway inflammation. Resveratrol is known to bind estrogen receptors; however, *in vitro* study using human epithelial cells showed that neither tamoxifen, an antagonist of estrogen receptors nor mifepristone, an antagonist of glucocorticoids altered the inhibitory effect of resveratrol.[12] These results suggest that resveratrol play an antiinflammatory role through a novel pathway. Therefore, further studies are needed to examine which immune cells can response to resveratrol and which pathways are involved in the inhibitory effect of resveratrol.

Although resveratrol is less potent compared to glucocorticoids, it appears to be more effective in suppressing inflammatory activity.[7,9,13] The clinical use of glucocorticoids has a high risk of side effects, and the effect of glucocorticoids is controversial, especially in noneosinophilic asthma. However, resveratrol has been shown to even suppress the development of noneosinophilic asthma.[10,14,15] Therefore, resveratrol and related compounds should be further investigated as alternatives to corticosteroids for the treatment of nonallergic forms of asthma. Resveratrol hold a great promise as a natural agent, since it has been shown to have beneficial effects in a variety of diseases, including cancer, cardiovascular disease, neurologic disorders as well as obesity. Therefore, the precise mechanisms of resveratrol are required to confirm the possibility of resveratrol as a therapeutic agent.

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